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Pilot study of the effect of lipophilic vs. hydrophilic beta-adrenergic blockers being taken at time of intracardiac defibrillator discharge on subsequent PTSD symptoms

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ABSTRACT

A pathophysiological model of posttraumatic stress disorder (PTSD) posits that an overly strong stress response at the time of the traumatic event leads to overconsolidation of the event's memory in part through a central β-adrenergic mechanism. We hypothesized that the presence of a β-blocker in the patient's brain at the time of the traumatic event would reduce the PTSD outcome by blocking this effect. The unpredictable, uncontrollable discharge of an implantable intracardiac defibrillator (ICD) is experienced by most patients as highly stressful, and it has previously been shown to be capable of causing PTSD symptoms. The present pilot study evaluated a convenience sample of 18 male cardiac patients who had been taking either a lipophilic β-blocker (which penetrates the blood-brain barrier) or a hydrophilic β-blocker (which does not) at the time of a discharge of their ICD. The self- report PTSD Checklist-Specific Version quantified 17 PTSD symptoms pertaining to the ICD discharge during the month preceding the evaluation. There was a statistical trend for patients who had been taking a lipophilic β-blocker at the time of the ICD discharge to have (35%) less severe PTSD symptoms than patients who had been taking a hydrophilic β-blocker (one-tailed $p = 0.07$, $g = 0.64$). Further, prospective, randomized, controlled studies are suggested.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a mental disorder that may result from exposure to an extreme, psychologically traumatic event. A cardinal feature of PTSD is strong, durable, intrusive, and distressing memories of the event, which in some cases may persist for a lifetime (Orr, Pitman, Lasko, & Herz, 1993). A number of endogenously released or exogenously administered stress-related hormones, including epinephrine and cortisol (corticosterone in rodents), have been found to strengthen memory consolidation in laboratory experiments (McGaugh, 2013; Roozendaal & McGaugh, 2011). The intense fear, helplessness, and/or horror in response to the traumatic event typically experienced by persons who go onto develop PTSD are likely accompanied by the endogenous release of stress hormones. We have hypothesized that such hormones, by overly strengthening consolidation of the memory of the traumatic event, may be involved in the pathogenesis of PTSD, reflecting an overshoot of an ordinarily adaptive mechanism (Pitman, 1989). Systemic administration of the lipophilic β-adrenergic blockers propranolol and metoprolol, which are capable of crossing the blood–brain barrier, has been found to oppose the potentiation of memory consolidation by stress (Cahill, Pham, & Setlow, 2000; Cahill, Prins, Weber, & McGaugh, 1994; O'Carroll, Drysdale, Cahill, Shajahan, and Ebmeier, 1999) and stress hormones (McGaugh, 2013; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006) through a final common pathway. In contrast, systemic hydrophilic β-blockers such as sotalol and nadolol, which do not cross the blood–brain barrier, typically have been found not to exert such an effect (Introini-Collison & Baratti, 1986; Robinson & Franklin, 2007).

If the above hypothesized pathogenic model of PTSD is valid, then the administration of lipophilic β-blockers following the occurrence of a traumatic event might reduce the likelihood of subsequent PTSD by blocking stress-induced overconsolidation of the traumatic memory. This has been investigated in several studies that have employed propranolol, with positive (Vaiva et al., 2003),

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negative (Stein, Kerridge, Dimsdale, & Hoyt, 2007), and mixed (Hoge et al., 2012; Krauseneck et al., 2010; Nugent et al., 2010; Pitman et al., 2002) results. One possible reason for failure to observe a PTSD preventive effect of propranolol is the delay between the traumatic event's occurrence and the administration of the drug, which in some of the above studies was a day or longer. The susceptibility of memory consolidation to noradrenergic influences, which propranolol antagonizes, has been shown to be restricted to a time window, which may only consist of several hours (Gazarini, Stern, Carobrez, & Bertoglio, 2013). It is possible that in the above studies, the propranolol exerted its effect too late to significantly oppose excessive memory consolidation induced by the traumatic stress, thereby precluding a valid test of the hypothesis. It is possible that propranolol, or other lipophilic β-blockers, administered sooner would be more effective. Even more effective might be β-blockers that are already on board at the time the traumatic event.

Intracardiac defibrillators (ICDs) have been successfully surgically implanted in humans since 1980. Recent models allow for office-based, subcutaneous implantations. The battery-powered ICD monitors heart rhythms and automatically discharges an electrical impulse (shock) to the heart when an abnormal, potentially fatal rhythm is detected. These devices have been shown to decrease mortality from cardiac causes and have been prescribed for millions of patients with histories of potentially fatal arrhythmias, myocardial infarction, congestive heart failure, and other cardiac risk factors (Al-Khatib et al., 2013).

ICD discharges are often experienced as highly stressful, and they have been found to be associated with subsequent PTSD symptoms (Sears & Conti, 2003). Some patients have described them in dramatic terms, e.g., "like being kicked in the chest by a mule." Syncope or other brief physical incapacitation may even occur. In addition to the upsetting nature of the unpredictable, uncontrollable discharge itself, the fact that an ICD discharge has occurred may alert the patient to the possibility that a life-threatening event has taken place, or even worse is still taking place, in their heart, thereby increasing the traumatic psychological effect. Sometimes a series of ICD discharges, or "storms," may occur, multiplying the trauma. ICDs may also discharge spuriously, i.e., in the absence of an arrhythmia, and the patient may not know the difference. Both warranted and spurious discharges have been characterized as stressful in cardiac patients' quality of life narratives (Ford, Sears, Shea, & Cahill, 2013).

Beta-blockers (including lipophilic drugs such as propranolol, metoprolol, and carvedilol, and hydrophilic drugs such as atenolol and sotalol) are part of the preventive cardiology armamentarium. Most patients with ICDs are prescribed one or more lipophilic or hydrophilic β-blockers. Because such patients would already be taking β-blockers at the time an ICD discharge occurred, they may offer an opportunity to test the putative, central PTSD preventive effect of lipophilic β-blockers that is free of the problem of a delay between the traumatic event's occurrence and the administration of drug. It is possible that the peripheral effects of β-blockers alone could confer prevention against PTSD, e.g., according to a James-Lange type mechanism, in which diminished perception of peripheral physiological arousal due to the drug reduces fear. Including patients who were taking hydrophilic β-blockers at the time of ICD discharge in the scientific design provides a control for this possibility, given that the anti-adrenergic effects of hydrophilic β-blockers are at least as great as those of lipophilic β-blockers (Kardos et al., 1998).

The present, retrospective pilot study evaluated PTSD symptoms related to an ICD discharge event that occurred in cardiac patients who were taking either prescribed lipophilic or hydrophilic β-blockers at the time of the discharge.

2. Methods

2.1. Subjects

Subjects comprised a convenience sample of 18 male outpatients. (Too few female subjects could be recruited to form an analyzable group.) Each subject had been seen for a visit at least once at the Massachusetts General Hospital (MGH) Cardiac Arrhythmia Clinic during the year preceding the study, and each had experienced at least one ICD discharge sometime in the past, excluding "test shocks" (in which the device was interrogated within a controlled hospital setting in a predictable fashion expected by the patient). In order for a patient to be included, it was necessary both that the medical records documented that the patient had been prescribed a β-blocker at the time of the "index" ICD discharge, and that the patient confirmed that they were taking the medication at the time.

Prior to contacting subject candidates, the electronic medical record, including entries from all disciplines including psychiatry, was reviewed for potentially excluding factors. All subjects had been followed at the MGH for at least three years. All had been screened for psychiatric disorders using standard questions, the results of which were entered in the record. The exclusion criteria included: age <18 years; any pre-existing DSM-IV (American Psychiatric Association, 1994) Axis I mental disorder, including PTSD from another traumatic event and substance abuse or dependence; or current medical illness that contraindicated participation (e.g., asthma). As shown in Table 1, two patients (both in the lipophilic β-blocker group) were taking benzodiazepine anxiolytics at the time of the index ICD discharge (DR and VO in Table 1).

2.2. Institutional Review Board approval and informed consent

Partners Healthcare Institutional Review Board (IRB) approval was obtained to (1) conduct chart reviews in order to identify eligible subject candidates, (2) mail a postcard requesting eligible candidates to contact the investigators if interested in participation, and (3) conduct telephone interviews of subjects who indicated an interest, including administration of a PTSD symptom questionnaire. After a full explanation of the study's procedures, written informed consent was obtained from all subjects on a form approved by the IRB.

2.3. Psychometric instrument

The Post-Traumatic Stress Disorder Check List (PCL) has been highly validated (Wilkins, Lang, & Norman, 2011), including in cardiac patients (e.g. Prudente, Reigle, Bourguignon, Haines, & DiMarco 2006). The correlation between total PCL score and total score on the Clinician-Administered PTSD Scale has been reported at $r = 0.80$ among several cohorts of medical patients. (Wilkins et al., 2011). The PCL is a self-report rating scale that comprises 17 items corresponding to the 17 DSM-IV diagnostic criteria for PTSD. A Likert-type scale (1–5) is used by the patient to report how much they have been bothered by each PTSD symptom during the past month, with 1 designating "not at all," and 5 designating "extremely." For this study, the PCL-Specific (PCL-S) version) (Weathers, Litz, Huska, & Keane, 1994) was used. This version pertains to a specific traumatic event, in this case the ICD discharge. If a patient had experienced more than one ICD discharge, they were asked to identify the one that they remembered as having been most stressful for them, and the PCL-S was administered with reference to that ("index") event.

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